REMARKS

Claims 1 and 2 are pending in this application. Claims 3 and 4 were previously cancelled without prejudice or disclaimer. Claims 5-10 have been withdrawn from consideration as being drawn to a non-elected species.

1. Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1 and 2 are rejected under 35 U.S.C. § 112, first paragraph as allegedly containing material that "was not described in such a way as to reasonably to convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Applicants respectfully disagree.

It is respectfully submitted that the person of skill in the relevant art is an immunologist and that as such, the skilled practitioner would understand from the description in the specification and examples that the interaction of the claimed monoclonal antibody with a fusion protein containing a his tag is specific binding at an epitope within the fusion protein that is absent in a similar polypeptide lacking the his tag. The skilled practitioner would understand that the epitope is clearly at the his tag, since the specification teaches at page 3, ¶ 2, that the antibodies of the invention "distinguish themselves in that they recognize any fusion polypeptide comprising a histidine portion." In any discussion of antibodies, the term "to recognize" is understood to mean "to bind." In order for all of the antibodies of the invention "to recognize" "any" fusion polypeptide containing a his tag, the antibody must "recognize," *i.e.*, bind, the "histidine portion."

Furthermore, Example 3 expressly addresses the specificity of the antibody recognition. Example 3 exemplifies the specificity of the claimed antibody for His adm2 and lack of recognition for hdm2, which differ only in the presence of the his tag or any other protein present

in the assay. The antibody recognized only His adm2 and none of the other proteins in the assay that lacked a his tag, including adm2, *i.e.*, there was no cross-reactivity . Thus, contrary to the Examiner's assertion, the specification discloses that the antibodies do not bind to fusion proteins at the non-histidine portion of the protein. The only possible site of recognition of the fusion protein is at the his tag, a fact that any person of ordinary skill in the art would recognize from this disclosure. Antibody recognition of epitopes is a well understood natural phenomenon, and the process by which monoclonal antibodies are made, which results in their specificity of recognition is well known to those of skill in the art. Thus, the example provided in the specification, which demonstrates the specificity of binding of the claimed antibody is generic to the class of antibodies claimed.

Although the language of the claims is not present in the specification *ipsis verbis*, and indeed, there no such requirement under 37 C.F.R. § 112, first paragraph, one of ordinary skill in the art would recognize that the claimed monoclonal antibody must bind to a site that is only present in all his tagged fusion proteins, *i.e.*, at the his tag. Thus, the claims meet the requirements of 37 C.F.R. § 112, first paragraph.

Accordingly, the rejection of claims 1 and 2 under 35 U.S.C. § 112, first paragraph is respectfully traversed.

2. Claim rejection under 35 U.S.C. § 103(a)

Claims 1 and 2 are rejected under 35 U.S.C. § 103(a) over Evans et al. in view of Randall et al. and further in view of Harlowe et al. as allegedly being unpatentably obvious. The Examiner states that Evans teaches polyclonal antibodies that specifically recognize metal binding tags present in fusion proteins and asserts that the only difference between Evans et al. and the present invention is that Evans' metal binding tags are not his tags. The Examiner relies

on Randall as teaching a metal binding tag including six successive histidine residues and Harlowe as teaching a method of producing monoclonal antibodies. The Examiner concludes, therefore, that it would have been obvious to one of ordinary skill in the art to have made the claimed monoclonal antibodies having specificity to a his tag present in the fusion protein.

Applicants respectfully disagree for at least the following reasons.

Evans discloses antisera containing polyclonal antibodies that recognize recombinant proteins containing a metal binding peptide (mbp tag). The data presented in Figure 3 of Evans demonstrate that antibodies to the mbp tag have significantly different affinities for the epitope (see proteins 1 and 2), while some of the antibodies are not specific for the mbp tag at all and actually cross-react with a his tag (see protein 5). Thus, Evans' results indicate that antibodies to a mbp tag are unreliable and do not provide specificity to the mbp tag, contrary to the Examiner's assertions otherwise. As a result, the skilled practitioner would not have been motivated, as the Examiner asserts, to substitute the his tag for the mbp tag, since the latter provides unsatisfactory results and demonstrates that there is cross reactivity between antibodies to the two epitopes, indicating that use of such tags provides unreliable results.

The Examiner's reliance on Randall does not cure the inadequacies of the primary reference. Although Randall discloses use of a mbp tag containing six consecutive histidine residues, Randall's data show that use of such mbp tag was not successful. The Western blot shown in Figure 5 of Randall does not **show any** discernable labeled peptide in either of columns #1 (His-p17-Pk probed with anti-His-Rt-Pk serum) or #2 (His-P17 probed with anti-His-Rt-Pk serum). The authors allege, but do not show, that longer exposures indicate the presence o f some antibody to the his tag. However, if such antibodies even existed in the Randall antisera, it

is clear from the data in Figure 5 that such antibodies are very few in number and obviously difficult to obtain (or detect).

Moreover, the tag used by Randall was actually a twelve amino acid tag containing six consecutive histidine residues, but the remaining amino acid sequence of the tag was not provided. Thus, one of skill in the art cannot determine from the cited prior art article whether the histidine portion of Randall's tag was responsible for the weak anitigenicity that Randall refers to (but does not demonstrate) or whether the (unshown) antibodies recognize other sequences within the tag.

Moreover, the antibodies obtained by Randall were not directed against a six amino acid his tag, but nonetheless demonstrated weak binding to such a motif. As such, Randall's results teach that such a his tag is a poor choice of epitope for developing antibodies, since it will result in non-specific binding with antibodies directed against other tags.

The combination of Evans and Randall, then, teaches that antibodies to his tags are not easily obtained (Randall, Figure 5), and even if obtained, they lack specificity and antibodies directed against other tags cross react with Evans his-containing tag (See Evans Figure 3). Thus, the combination of Evans and Randall actually teaches away from the claimed invention and clearly, does not disclose or suggest predictability of specificity of antibodies raised against his tags. As such, the skilled artisan would not have been motivated to substitute Randall's tag element, for Evans' non-specific mbp tag element, to develop a monoclonal antibody as taught by Harlowe, with the expectation that such antibodies would be obtainable and/or exhibit epitope specificity.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

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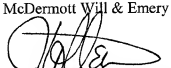

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